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ABSTRACT

There is a growing body of evidence that Sudden Infant Death Syndrome (SIDS) victims are not completely normal and healthy, as was once believed. A variety of new information from several disciplines strongly suggests that the infant who dies suddenly and unexpectedly may do so because of subtle developmental, neurologic, cardiorespiratory, and metabolic defects that converge at a particularly vulnerable time. Associated factors may include the anatomic structure of the upper airway, upper respiratory infection, and stress-producing environmental conditions. This report on SIDS first presents the historical perspective, the epidemiology, and the etiology of the phenomenon and describes the research efforts of the National Institute of Child Health and Human Development. The second section outlines the current stage of knowledge about SIDS including recent pathologic findings and findings on the role of sleep. In the final section, recommendations are made for research in the areas of epidemiology, infection and immunology, metabolic factors, upper and lower airways, behavioral considerations, sleep, biochemical factors, and the central nervous system. A bibliography of 77 references is included. (JD)

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Sudden Infant Death Syndrome

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SP 020 560

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Sudden Infant Death Syndrome

I. Introduction

Historical Perspective

The earliest written record of sudden and unexplained infant death, in all probability, appears in the Bible--"and this woman's child died in the night; because she overlaid it."[1] Later references to sudden infant death occurred during the Middle Ages and can be found on gravestone inscriptions. Although there is no way of confirming that the references were to the entity known today as the sudden infant death syndrome (SIDS) or "crib death," it is likely that a number of them were to that phenomenon. Before the 1900s, when SIDS was not recognized as a distinct entity, high infant mortality resulting from infectious diseases, malnutrition, and respiratory and metabolic conditions could easily mask such deaths. There is no doubt, however, that apparently healthy infants died suddenly and unexpectedly while they slept and that their deaths were ascribed in each case to some cause, usually pneumonia, suffocation, or neglect, depending on social status.

With the rise of the thymic theory in the mid-1800s,[2] it was suggested that healthy infants and children could die suddenly and unexpectedly because of an enlarged thymus. Cause of death was attributed not to suffocation, neglect, or trauma, but to a specific pathologic condition that could be seen at autopsy, and for a few decades, parents, wet nurses, or nursemaids were not automatically blamed or accused, as was once the case, of neglect or dereliction of duty.[3] The thymic theory, however, became less acceptable in the second half of the 1800s, and sudden infant deaths were again attributed to overlaying, suffocation, and neglect.

A complete description of infants who died suddenly and unexpectedly is given by Templeman in an 1892 paper on 258 cases.[4] His description is in part strikingly similar to today's pathologic findings.

> The external appearances presented by the body are chiefly of a negative character. There are no marks of violence to be observed. As a rule there is no flattening of the nose and face from pressure. Post-mortem lividity comes on early, and is specially well marked on that side of the body on which the infant has been lying; the face is placid and calm; the eyes sometimes slightly congested, but not staring; the lips are livid, and the tongue not protruded. Frothy mucus, often tinged with blood, is generally seen about the mouth and nostrils. The hands are sometimes tightly clenched . . . . A complete or partial examination presented the usual appearances found in cases of death by asphyxia, viz., a varying degree of congestion of the cerebral membranes--more or less engorgement of the internal organs, especially the lungs and kidneys, and the large thoracic veins, a fluid condition of the blood, which was dark in colour; and generally a distended condition of the right side of the heart, while the left was nearly or altogether empty and contracted . . . . In about half the cases examined small punctiform haemorrhages were observed beneath the pleura and pericardium. The larynx, trachea, and bronchi were, as a rule, congested, and contained some frothy, often blood-stained mucus. (p. 324)

Templeman also reported that the greatest number of observed cases occurred between October and March, that the greatest incidence was found among infants from 1 to 6 months of age, and that the incidence was highest in families of low socioeconomic status. Templeman believed the infants died from overlaying, which he attributed to ignorance, carelessness, drunkenness, and overcrowding.

Systematic study of SIDS began in the 1940s. Between 1942 and 1953, Werne and Garrow[5-8] published a series of papers providing important evidence that, in many cases, death was caused not by suffocation but by another mechanism, probably inflammation. The data reported by these investigators served as an impetus for further study of SIDS infants and led to the accumulation of important epidemiologic and pathologic data.

Early Federal Effort

Federal involvement in research on SIDS began when the National Institute of Child Health and Human Development (NICHD) conducted an international conference in Seattle, Washington, on September 9-10, 1963.[9] The conference identified the need for Federally supported research on the epidemiology, pathogenesis, and etiology of SIDS, and it resulted in the following consensus conclusions: (1) SIDS occurs in all socioeconomic groups, although there seems to be a socioeconomic gradient, with higher frequency in lower income groups; (2) the incidence is about the same in several parts of the United States and similar to that in England; (3) the evidence relative to seasonal and sex incidence is unclear; (4) a correlation with the occurrence of infectious disease in the general population is uncertain; and (5) although multiple cases in a single family have been reported, no clear evidence as to whether such occurrences were coincidental is available. The conferees agreed that the period between 2 and 5 months of age might well be a transitional one between "neonatal and more mature infant responses" and that changes in responses during this period merited considerably more study.

A second international conference on causes of SIDS was sponsored by the NICHD in 1969, also in Seattle. Its major focus was on epidemiology, although considerable attention was given to pathology and to viral infections as possible causes. Two papers addressed physiologic considerations. An important contribution of this conference was a definition of SIDS:

> The sudden death of any infant or young child, which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death. (p. 18)[10]

Although this definition, which continues to be used, might well apply to a number of fatal syndromes not yet identified, it has the advantage of not requiring a set of specific histologic or cytologic findings to justify a diagnosis of SIDS.

While a diagnosis is still arrived at by exclusion, situational and postmortem clues in the majority of cases now permit one to be made with considerable certainty. SIDS characteristically occurs unobserved, usually during sleep, and predominantly among infants between the ages of 1 and 6 months. A high incidence of minute intrathoracic petechiae is usually found in victims who are otherwise free of abnormal tissue changes in this area. It may be that SIDS occurs among infants with other diseases, but this possibility cannot be dealt with effectively under the current exclu-

sional criteria. Diagnosis continues to be complicated by several difficulties:

- There is a lack of agreement about criteria that should be applied in making a diagnosis. Consensus among pathologists concerning the specificity of different lesions has not been and may never be achieved.
- Usually a considerable period of time, often indeterminate, elapses between death and postmortem examination, complicating the interpretation of biochemical and pathological findings. Death usually occurs between the hours of 9 p.m. and 6 a.m.
- Information is insufficient on normal human development in the postneonatal period. Many deficiencies in knowledge exist in pertinent areas such as developmental patterns in the central and autonomic nervous systems.

Summary statements included in the proceedings of the second international conference[10] outlined several multidisciplinary areas for general exploration to develop hypotheses that could be investigated and tested productively. Among the areas were: developmental cardiopulmonary physiology and neurophysiology; developmental aspects of immune response mechanisms; infection as a contributing factor in SIDS; pathology; and epidemiology.

The epidemiology summary identified two key questions: (1) Do SIDS victims have some underlying "disease" that has not yet been recognized and (2) do SIDS victims represent a random sample of the population, or are there identifiable factors that could define a high-risk population?

With regard to the first question, the evidence seemed to indicate that it was unlikely that a "particular underlying disease in the ordinary sense" was involved. As to the second, evidence presented during the conference established that SIDS victims occurred in the population generally, but not in a random manner. It was the consensus of the 1969 conference that SIDS victims are essentially "normal" and that they appear to be going through a stage of increased, seemingly physiological, vulnerability marked particularly by the presence of certain characteristics that act either independently or in concert with other factors.

Broadening the Research Base

The proceedings of the 1969 conference guided the NICHD staff in efforts to plan a comprehensive approach to re-

search. Seven areas were identified for emphasis: (1) developmental neurophysiology with emphasis on sleep patterns and associated autonomic disturbances that may interfere with vital functions; (2) respiratory, cardiac, and laryngeal responses to specific stimuli; (3) metabolic, thermal, and endocrine factors; (4) perinatal development of immune-response mechanisms and infectious disease processes; (5) psychological stresses experienced by parents and siblings when a SIDS event occurs; (6) epidemiologic, environmental, and genetic aspects; and (7) anatomic pathology.

Research planning workshops were convened to explore these areas, determine the state of the art regarding SIDS, develop tentative hypotheses to be tested, and identify investigators who might be encouraged to undertake SIDS research in areas of special interest. By 1977, 41 research grants and contracts, representing a variety of basic and clinical disciplines, but specifically concerned with SIDS, were being supported by the NICHD.

Epidemiology

Numerous epidemiologic studies of the sudden infant death syndrome have been conducted over the past two decades. Frequently observed attributes, as indicated previously, have been identified, including: peak incidence between 1 and 4 months of age; higher rates in males than in females; low socioeconomic status; higher rates among low-birthweight infants; highest incidence in cold weather months; and silent death, presumably during sleep. A number of possible risk factors have also been determined,[10-12] including: prematurity; a sibling who died suddenly and unexpectedly of unknown cause; a twin; a history of recent mild upper respiratory infection; inadequate maternal prenatal care; and nonwhite race. The number of factors provides a good indication of the complexity of the task.

Because SIDS is identified post mortem, epidemiologic studies of necessity have been retrospective. Typically, the investigation identified a group of SIDS cases and compared them with control groups, of which several kinds have been used. In some studies, the controls were samples of live-birth survivors. In others, each SIDS infant was matched with a live-birth survivor on the basis of such attributes as age, sex, and place of residence. Infants dying in the postneonatal period from presumptive non-SIDS causes have also been used as controls. Each of these kinds of controls is appropriate; selection of what kind depends upon the questions being asked in a given study.

If all pathologists collected the same data and considered the same set of alternatives, diagnoses of SIDS would

be more consistent. Variations in jurisdictions, however, present an obstacle. The Office of Maternal and Child Health in the Bureau of Community Health Services and the NICHD have made a considerable effort to obtain agreement from forensic pathologists (including medical examiners) on a standard necropsy protocol in order to determine a uniform approach to the diagnosis of SIDS. Although a provisional protocol has been developed, it is not generally followed by coroners or medical examiners.

The national incidence of SIDS is low (between 1.5 and 2 cases per 1,000 live births), but it accounts for at least one-third of postneonatal deaths up to 1 year of age. Given the absence of warning symptoms, prevention of SIDS depends to a considerable extent on the identification of antemortem factors that define infants at high risk for SIDS.

Etiology

Many hypotheses have been advanced to explain SIDS, and nearly all contemporary investigators would agree that multiple etiologies are involved, or at least that it would be unwise to rule out the possibility that several fundamentally different mechanisms could result in sudden and unexplained infant death. Several groups of etiologies have been suggested. One involves some type of failure in the development or maintenance of normal respiratory control, a related group focuses generally on sleep and in particular on sleep apnea, and another is concerned with interaction of one or more infecting agents upon a peculiarly susceptible immunological or other defense system. A fourth proposes that one or more biochemical defects may be important factors. Research in the last area has focused on the role of enzymes concerned with carbohydrate metabolism and on possible abnormalities of neurotransmitters.

The NICHD Cooperative Epidemiologic Study of Risk Factors

The NICHD is currently conducting a multicenter, case/control, epidemiologic study of potential SIDS risk factors. Six data collection centers have been established in regions that include rural and urban populations of different income and ethnic composition. The Data Coordinating Center is at the University of Washington in Seattle. Data from about 800 SIDS cases and about 1,600 matched controls are being developed. One set of controls will be

matched by age; the second by age, birthweight (<2,500 g; >2,500 g), and race (black/nonblack). Complete SIDS case ascertainment has occurred during a 15-month "patient entry" phase. Comparable data on past events and experiences have been collected on cases and on controls through pretested interview questionnaires. The study involves public health nurses, coroners, medical examiners, a variety of hospitals, and private physicians. Additional data will be obtained from birth certificates and from prenatal, delivery, and postnatal medical records. These several sources will provide an array of epidemiologic, demographic, medical, behavioral, and environmental information for comparison and analysis. The data are expected to be of high quality and sufficiently "robust" to permit confident identification of significant risk factors. It is also hoped that the resulting information may help differentiate SIDS infants from those dying from other causes during the first year of life.

To assure diagnostic comparability, a necropsy protocol designed by the NICHD is followed so that standardized tissue blocks are procured, from which microscopic slides are made by the Pathology Coordinating Laboratory in San Francisco. Each member of a three-member Pathology Study Panel independently reviews the same set of microscopic slides on every case and categorizes the tissue specimens on three bases: (1) without lesions; (2) with lesions insufficient to cause death; and (3) with lesions sufficient to cause death.

II. Current State of Knowledge

There is a growing body of evidence that SIDS victims are not completely normal and healthy, as was once believed. A variety of new information from several disciplines strongly suggests that the infant who dies suddenly and unexpectedly may do so because of subtle developmental, neurologic, cardiorespiratory, and metabolic defects that converge at a particularly vulnerable time. Associated factors may include the anatomic structure of the upper airway, upper respiratory infection, and stress-producing environmental conditions.

The Role of Sleep

The impact of sleep on human physiology has occupied the attention of scientists for more than a century. Quantitative noninvasive studies of sleep were made possible in

relatively recent times with the development of electroencephalography (EEG), which permits continuous observation of electrical activity of the brain during sleep without disturbing the sleeper. Early EEG studies by Berger[13] revealed a consistent change in the brain waves of humans in the transition from wakefulness to sleep and vice versa. A number of subsequent studies reported dramatic differences in sleep EEG patterns depending upon the time of night and the duration of sleep.[14] A concern with the chronologic course of events developed when Aserinsky and Kleitman[15] observed the occurrence of rapid eye movements (REM) during sleep in human adults. This observation, together with the additional discovery that dream recall is high when eye movements are present, focused new attention on the course of temporal events and physiologic concomitants of REM dream periods during sleep. An extremely important early observation was made by Jouvet and Michel[16] when they noted that the electrical activity of muscles in cats is quite high in non-REM sleep periods but is totally suppressed during REM sleep. These findings were confirmed in humans by Berger[17] in 1961. These key discoveries suggested for the first time that sleep is not a unitary state, and they led to the further discovery that there are two states of sleep in adults. Observations of 8-hour sleep periods in man by Dement and Kleitman[18] identified four stages of sleep and demonstrated that the four stages appear to alternate in a cyclic fashion. These sleep stages are described by the voltages emitted by the brain as an individual enters into, progresses through, and terminates sleep. Subsequent work by Oswald[19] and Jouvet[20] demonstrated the brainstem origin of REM sleep, and they proposed that the REM period is one kind of sleep and that all other periods of sleep, although involving several very different EEG patterns, represent another type.

Three states of sleep have been described in infants:[21] REM sleep, characterized by rapid eye movements, body movements, irregular respiration, suppressed electrical activity of muscles, and low-voltage, fast EEG activity; quiet sleep (QS), characterized by the presence of regular respiration, high muscle electrical activity and high voltage, and slow or trace alternate EEG activity in the absence of rapid eye movements and of body movements; and indeterminant or undifferentiated sleep (IS), consisting of a combination of REM and QS criteria with breaks in pure REM and QS and also transitions between REM and QS.

Differences in the characteristics of sleep in infants and in older children and adults have been observed by several investigators.[21] In infants born before the 40th week of gestation, REM sleep predominates over Q sleep. As the infant approaches the term gestational age of 40 weeks, the percentage of REM sleep decreases and the percentage of

Q sleep increases; at 41 to 44 weeks of gestational age, the proportion is about equal. With further maturation, the proportion of REM sleep continues to decrease relative to that of Q sleep. In infants born to narcotic addicts, the distribution of sleep states has been shown to deviate from the normal pattern. Newborn infants, chronically exposed in utero to low doses of methadone with or without concomitant heroin, have displayed more rapid-eye-movement sleep and less quiet sleep than control infants.[22]

From its earliest descriptions, SIDS has been associated with sleep, and the first SIDS studies supported by the NICHD, beginning in 1971, focused on the role of sleep in SIDS and particularly on the characteristics of sleep in normal infants and in infants who on the basis of epidemiologic data were considered to be at high risk. The earliest studies described the developmental pattern of sleep states in infants and cardiopulmonary regulation during sleep.[23] Investigators involved in this effort observed distinct developmental differences in mean heart rate, and to a lesser extent in mean heart-rate variability, between normal infants and subsequent siblings of SIDS victims considered to be at increased risk for SIDS. Heart rate of the subsequent siblings was found to increase more markedly than that of control infants during the first month of life in both Q and REM sleep states. Heart rate of the risk group was also higher at 3 months of age, particularly when the infants were awake. Heart-rate variability in the high-risk group did not increase as it did in normal infants during the age period of 1 week to 2 months.

These observed differences may reflect delayed maturation or impaired functioning of the autonomic nervous system, and particularly of the control of the vagus nerve, in the high-risk group. Some of these differences, however, might also be due to chronic hypoxia. The tendency of the differences to be most pronounced when the high-risk infants were awake supports the possibility that oxygen regulation was impaired. It is therefore possible that both chronic hypoxia and a dysfunction in autonomic control which might result from it play a significant role in precipitating the SIDS event.[23]

Infants with prolonged episodes of apnea and bradycardia who require, or are thought to require, resuscitation have been described in the literature as "near miss for SIDS."[24] Several "near-miss" infants have subsequently died of SIDS. A team of investigators has conducted 24-hour polygraphic monitoring of "near-miss" infants and normal control infants.[25] Several types of respiratory events were measured including: central or diaphragmatic apnea, in which there was no passage of air through the upper airway and no movement of the chest wall; obstructive apnea, in

which there was no passage of air through the upper airway but the chest wall moved as if breathing were taking place; and mixed apnea, in which both obstructive and diaphragmatic apnea were involved. In mixed apnea, central apnea was either followed by obstructive apnea or intermixed with it.[26] Also measured was periodic breathing, which was defined as at least two central apneic events lasting less than 10 seconds but within 20 seconds of each other.[27] Analysis of these respiratory variables and comparison of "near-miss" and control infants indicate that between 3 weeks of age and 4-1/2 months of age only one variable was consistently different at a statistically significant level--the number of mixed and obstructive apnea periods of greater than 3-second duration during total sleep time. It is of special interest that in mixed apneas, the central apneic component consistently occurred first. In one "near-miss" infant who died of SIDS 36 hours after the recording, the total of mixed and obstructive respiratory pauses during total sleep time was the only significant abnormality noted in a 24-hour polygraphic monitoring.[28]

Since it cannot be known whether or not "near-miss" infants would have died, the term itself is questionable. There is increasing documentation of cases, however, in which such infants appeared to be quite well following the episode and yet died subsequently of SIDS, sometimes within a week. It has been suggested that infants having episodes of the type described are at high risk for SIDS and that they should be evaluated fully and placed under surveillance.

The potential value and hazards in the use of monitoring systems in the home to give early warning of episodes that require resuscitative intervention are currently being investigated. Until the complex psychologic, physiologic, and technical aspects of this subject are better understood, home monitoring is recommended with caution by the Committee on Infant and Preschool Child of the American Academy of Pediatrics.[29] Recognizing the potential morbidity and possible mortality associated with prolonged apneic periods, the Academy's Task Force on Prolonged Apnea recommends, in addition to specific treatment for the underlying disorder, 24-hour surveillance, including intensive observation by skilled caregivers trained in infant cardiopulmonary resuscitation. Electronic monitoring of the heart and(or) respiratory rate used under medical supervision is proposed as a useful adjunct to the recommended 24-hour surveillance.

Pathologic Findings

Postmortem studies of SIDS have had an important role in changing the focus of SIDS research from a preoccupation

with the events immediately surrounding death to a determination of abnormalities in the infants antedating death. At least two-thirds of SIDS victims have a variety of subtle abnormalities, such as: (1) abnormalities in the mechanisms that control respiration; (2) abnormalities that may be the consequence of the noxious events that have damaged the respiratory control mechanisms; and (3) abnormalities that currently have an unknown relationship to the deaths.

Chronic Alveolar Hypoxia

About 60 percent of SIDS victims have an increased mass of muscle in their small pulmonary arteries. Presumably caused by a chronic underventilation of the lungs, the finding was initially questioned but has now been confirmed by three independent investigations. Underventilation reduces the level of oxygen in the air spaces of the lungs and causes nearby arteries to constrict. When the constriction is prolonged, the number of muscle cells in the walls of the arteries increases.

Increased muscle and constriction of the pulmonary arteries increase the resistance to blood flow, which in turn forces the pressure to rise in the right ventricle of the heart. The heart responds like the pulmonary arteries by increasing the amount of muscle in the right ventricular wall. Although "a distended condition of the right side of the heart" was described by Templeman[4] in 1892, the actual abnormalities of both the pulmonary arteries and the heart were overlooked for many years in cases of SIDS because the analyses that are necessary for recognizing them are not included in routine postmortem examinations.[30,31]

Chronic Hypoxemia

The underventilation that presumably reduces the level of oxygen in the pulmonary air spaces leads to chronic hypoxemia. The consequences of such hypoxemia are found in more than half of SIDS victims. One consequence is the production of red blood cells by the liver and an increase in the production of red cells in the bone marrow.[32] These effects are the presumed result of hypoxemic-induced release of erythropoietin from the kidney. Most SIDS victims have an abnormal increase in the specialized adrenal gland tissue that makes epinephrine.[33] An increase in the release of epinephrine from the adrenal gland may explain the retention of brown fat in about half of SIDS victims.[34] Brown fat

usually reappears in adults who have a high level of epinephrine in the blood as a result of an adrenal tumor or chronic hypoxemia.

SIDS victims are not abnormally small at birth but they frequently lag in growth after birth. The growth pattern of their organs resembles that seen in experimental animals that are maintained postnatally in an hypoxic environment and is quite unlike the growth pattern resulting from undernutrition. Still another sign of hypoxemia in about half of SIDS victims is an increased level of the adrenal hormone cortisol that normally rises in response to hypoxemia and other forms of stress.

Chronic Underventilation

There is evidence that the underventilation of the lungs of SIDS victims is the result of abnormalities in the mechanisms that control respiration. Steinschneider[35] and Shannon et al.[36] have observed chronic underventilation and blunted respiratory responses to increased levels of inhaled carbon dioxide in such infants. Haddad et al.[37] observed an increased ventilatory response to 2 percent carbon dioxide (CO_2) in "near-miss" infants during sleep. These observations suggest that infants at high risk may have abnormalities in the control centers of the brainstem, which normally respond to accumulations of CO_2 by increasing the frequency and depth of respiration.[35,36,38,39]

Abnormal proliferation of astroglial fibers is present in about half of SIDS victims in many areas of the brainstem, including the lateral reticular formation, which is a key center for the control of respiration.[33] Takashima and his associates[40] recently found that astroglial proliferation is greatest in SIDS victims in the areas of the brain where the blood supply is poorest. This finding strengthens the view that the astroglial proliferation is the result of hypoxemic injury rather than the cause of abnormalities in respiratory control.

Recently Quattrochi[41] reported that neurons in the pons and medulla of SIDS victims have abnormally retained reticular dendritic spines. The neurons that exhibit these dendritic spines are believed by some investigators to regulate respiratory rhythms. Quattrochi suggests that the abnormally retained spines reflect a delay in the maturation of the affected dendrites; to date, however, there has been no confirmation of Quattrochi's findings.

Abnormalities in carotid bodies may be responsible for the ventilatory abnormalities in some SIDS victims. In the early months, during rapid-eye-movement sleep, the lungs partly collapse, the intercostal muscles do not move, and if

the diaphragm also stops moving, little residual air remains in the lungs to continue the normal exchange of oxygen and carbon dioxide. The result is hypoxemia within a few seconds. When breathing stops, the reflexes that in older children augment or restart breathing are notably less active in young infants. The survival of these infants, therefore, depends on a reflex arousal out of REM sleep and a switching on of the brainstem mechanisms that restart breathing. The carotid body has an important role in both functions. It has been discovered that more than half of the victims of SIDS have an underdeveloped carotid body.[42] If the organ is not functioning normally, the infant may not be able to restart its breathing during a prolonged episode of apnea. Sudden death victims who have underdeveloped carotid bodies usually have postmortem signs of antecedent chronic underventilation and hypoxemia. Lack of stimulatory impulses from the brainstem is one possible explanation for the underdeveloped carotid bodies in SIDS victims.

Nonventilatory Abnormalities

The brainstem centers that control respiration are very close to structures that control other body functions, so any defect impairing the respiratory control mechanisms might also affect other functions. In fact, nonrespiratory impairments are found in a portion of SIDS victims, and most of them point to dysfunctions centered most likely in the brainstem. Thus, long before death, some SIDS victims have abnormalities in temperature regulation, feeding, motor tone, and neurologic reflexes,[43] and some have an abnormal cry and react with subnormal intensity to various environmental stimuli.[44] Orlowsky and others[45] recently recorded markedly abnormal brainstem auditory evoked potentials in 13 infants who had life-threatening apneas and showed clinical characteristics thought to be criteria for high-risk SIDS. Infants who had repeated hypoxic or hypoxemic episodes for other reasons, however, did not have abnormal brainstem auditory evoked potentials. These observations suggest that the abnormalities in the SIDS victims were not the result of postnatal hypoxemic damage to brainstem structures. It has recently been found postmortem that levels of the major neurotransmitters are normal in the brains of SIDS victims.[46] No deficiencies were found in SIDS victims by comparison with the controls.

Abnormalities of the Central Nervous System

The presence of some of the abnormalities in newborn SIDS victims indicates that some dysfunctions in the central

nervous system (CNS) may be genetic in origin or may be the consequence of injuries during pregnancy, labor, or delivery.[45,47] Studies have found no evidence that SIDS victims as a group are subjected to greater intrapartum hypoxia, trauma, or damage from neurotoxic anesthetic agents than are other infants.[47] These findings raise the possibility that brain abnormalities in some victims are genetic in origin or that brain damage occurs during fetal life. There is considerable evidence of a genetic component in some families that have lost several infants to SIDS.[36] Zwillich and others[48] have reported that parents of SIDS victims almost always have a normal ventilatory response to hypoxia and to hypercapnia. He has also reported that such parents have normal respiratory frequencies, tidal volumes, inspiratory times, and arterial blood gas tensions. In contrast, other investigators have found such abnormalities in the parents of a few SIDS victims. Thus, the question of genetically linked abnormalities in respiratory control as a possible cause of SIDS is unsettled.

If SIDS is usually an acquired disorder in which the brainstem is damaged, when does the damage take place? Amniotic fluid infections have been found sometimes to cause mild CNS damage in fetuses and neonates.[32] Maternal cigarette smoking reduces placental intervillous blood flow, retards fetal growth, and may impair children's mental performance.[49] The brainstem is a particularly vulnerable target. Both hypoxia and hypoglycemia can damage brainstem nuclei in the perinatal period,[50-52] and it has been suggested that hypoxia may play a role in the brainstem damage in some cases with congenital cranial nerve palsies.[53] It is conceivable that SIDS victims, similar to those with congenital cranial nerve palsies, have had a brainstem insult in utero or in the perinatal period. Barbiturates reportedly can retard brain growth in experimental animals.[54]

Pathophysiology of Cardiorespiratory Function

Two studies have demonstrated thickening of the media of the pulmonary arterial blood vessels in some infants dying of SIDS. The studies indicate that the victims sustained at least one abnormality over a prolonged period.[55,56] As a result of this finding, the assumption has been made that some SIDS victims have been chronically hypoventilating. It remains to be proved, however, whether this explains the pulmonary vascular findings.

As discussed earlier, "near-miss" infants have a demonstrated increased heart rate and decreased beat-to-beat variability.[57] These infants have also demonstrated an

abnormality in the conduction time of the electrical impulse in the heart (QT interval)[58] and a normal or increased ventilatory response to 2-percent CO_2 during sleep.[37] Although the precise reason for these findings in "near-miss" infants has not yet been determined, one possible explanation is an increase in sympathoadrenal activity. Siblings of SIDS infants have also demonstrated increased heart rate and decreased heart-rate variability.[23] An increase in respiratory rate has also been found in this group.[59] An increase in the number of obstructive and central apneas in "near misses" has also been reported.[60]

An understanding of the pathophysiologic alterations in SIDS depends upon a clear delineation of normal physiology during maturation and sleep. There is a sleep-state effect on ventilation, heart rate, and QT interval.[61-65] The response of an infant breathing air with a reduced oxygen content depends not only on sleep state and maturation; it is also related to age at the time of exposure to an hypoxic environment. Thus, an initial but transient increase in ventilation in response to hypoxia, followed by a decrease in ventilation, has been noted in very young infants.[66] Young infants at high altitudes are also unable to sustain an increase in ventilation in response to hypoxia.[67] Older infants do not demonstrate a subsequent depression of ventilation in response to hypoxia. Other studies have demonstrated that there is a maturation in the ventilatory response to CO_2 during sleep in primates. Thus, maturation of the infant appears to increase its sensitivity to CO_2 in respired air during quiet sleep.

Biochemical and neurophysiologic studies have demonstrated that, by adult standards, the response of the autonomic nervous system of the prematurely born infant is itself immature[68] and that such infants depend more on the renin angiotensin system for blood pressure control and defense against hypotensive stress.[69] Other studies have demonstrated that premature infants with apnea, another group believed to be at high risk for SIDS, have a decreased urinary excretion of catecholamines and catecholamine metabolites.[70]

Significant progress has been made recently in understanding the role of upper airway receptors in cardiorespiratory control and specifically in the genesis of serious apnea, bradycardia, and hypotension. The upper airway is richly innervated with receptors; when stimulated they are capable of producing marked changes in or inhibition of respiratory and cardiac function, as well as alterations in distribution of blood-flow rates,[71,72] decreased beat-to-beat variability, shorter QT intervals, and an increase in ventilation in response to CO_2. Although the mechanisms responsible for this cluster of findings have not been

ascertained, a possible explanation is an increase in sympathoadrenal activity. The precise relationship between these findings and hypoxia remains to be elucidated, and research in this area is likely to be highly productive. A final area in which some progress has already been made relates to the role of neurotransmitters and circulating chemical mediators in cardiovascular and respiratory control.

Infection and Immunity Factors

The host response to exposure to antigens undergoes major developmental changes during the fetal and newborn periods. Although the impact of the large antigenic load at birth has long been recognized, it is becoming increasingly apparent that the fetus is not completely protected from such exposure. Microorganisms, pharmacological agents, or any of a wide range of environmental substances or metabolites may stimulate an immunologic response of the host. The immune reaction to a specific antigen may differ radically during the developmental period from that seen in an adult and may serve to jeopardize rather than protect the host. The two factors--primary encounters with a multitude of antigens, including infectious agents, and a rapidly developing immune response--may set the stage for the sudden infant death syndrome.

The SIDS infant at autopsy is characteristically well developed and well nourished. The blood frequently is unclotted. Petechiae are commonly found in the thorax--in the pleura and the thymus. In about 50 percent of SIDS cases, an inflammatory process is seen in the upper airway, either larynx and(or) trachea, or larynx and(or) bronchi. Morphologically it resembles a subacute process with relatively few neutrophils and mostly lymphocytes. About 30 to 50 percent of the lymphocytes are plasma cells, as identified by the methyl green pyronine stain. Lymphoid tissue is remarkably well preserved. The thymus is often large and the mesenteric nodes are plump--hence, the diagnosis that was popular during the 1920s and 1930s, "thymico-lymphatic syndrome."

Although SIDS does not have the wave-like incidence suggestive of a specific viral etiology, the syndrome follows a pattern similar to that of respiratory infections in general. The viruses that have been incriminated reflect the investigational techniques employed, and the techniques themselves favor respiratory viruses. The quantity and distribution of viruses in the victim, however, preclude a finding of overwhelming infection and suggest instead a "triggering mechanism."

Bacterial infection has been implicated by some investigators as either primarily or secondarily related to an onset of SIDS. The most recent example, reported by Arnon et al.,[73] is that one of its causes might be the fulminant manifestation of infant botulism, where death results from intestinal infection and toxin produced by Clostridium botulinum. Of the first 60 cases of infant botulism identified in California, 10 died, and the affected infants could not be differentiated from SIDS infants at autopsy. Current studies being pursued by these investigators seek to determine the ability of breast milk to protect against C. botulinum infection.

If an immune response mechanism is implicated in SIDS, the immunologic release of mediators from target cells (mast cells) in the upper respiratory tract may be involved.[74] The best understood, and perhaps most likely, mechanism for such mediator release is an IgE antibody-antigen reaction.

Although some information exists regarding total IgE levels, which are easily measured, not nearly enough is known about IgE antibodies in the first few months of life. Measurement of IgE antibody levels against various common viral and bacterial antigens and products should provide general information that might contribute to an understanding of SIDS etiology and develop new knowledge about responses of young infants to infectious agents. It is clear that the induction of an allergic response mediated by IgE depends not only on the IgE antibody level but also on how much IgE antibody is in the target cells in the areas in question, as well as on the level of IgG antibodies that could block the reaction. It is possible that similar IgE antibody levels could exist in two children but would lead to an anaphylactic response in only one because of the differences in IgG blocking antibody levels.

Another major aspect of control that is somewhat unexplored in the newborn is the influence on allergic response of the autonomic nervous system and the endocrine system, acting singly or together. Information is accumulating to indicate that the level of intracellular cyclic adenylic acid (cyclic AMP) is an important controlling mechanism in the release of mediators of anaphylaxis from human lung tissue (basophils and mast cells). Thus, increases in cyclic AMP levels abolish the response, whereas if levels are low the response can be triggered quite easily.

The level of cyclic AMP in target cells is controlled by a variety of means. They include the levels at which endogenous hormones such as epinephrine, presumably cortisol, and perhaps prostaglandins are maintained. It is known as well that the target cells in the lung have various receptors on their surfaces, and it may well be that the

responsiveness of the receptor rather than the level of circulating hormone is important. It has been shown, for example, that children with asthma have a poorly responsive receptor in terms of the response of their cell adenyl cyclase system to endogenous epinephrine. It is possible that the beta receptor may also be a problem in SIDS.

There is considerable evidence that many silent infections occur during pregnancy, affecting both mother and fetus and subsequently the young infant. Cytomegalovirus can be cultured from the cervix of 1 percent of pregnant women in the first trimester, 6 percent in the second, and 18 percent by term. These figures suggest reactivation of a latent infection rather than reinfection. When samples were collected from infants for culturing, 1 to 2 percent were found to be infected at birth. Within a few months after birth, this figure had risen to 10 to 15 percent. These infections had gone unnoticed in pregnant women until appropriate cultural techniques were applied.

It is indeed probable that many more infections remain to be discovered. Adenovirus, for example, has been found in the urine of 11 percent of pregnant women. Although these infections generally do not cause acute infectious phenomena, their role as triggering mechanisms in miscarriages, prematurity, intrauterine growth retardation, and SIDS may be significant. Mycoplasma, for instance, has been found in high incidence in the cervix and appears to be related in some way to fetal growth retardation.

The massive antigenic load of mother and infant applies not only to viruses but to bacteria, fungi, protozoa, and their products. Antigens are presented to the fetus, and particularly to the young infant, at a time when the immunologic mechanisms are undergoing their most dramatic changes. A broad array of techniques must be used to define the antigenic load and evaluate its significance. The complex response of the host must be analyzed and its individual components studied developmentally. A broad base in biological science is necessary for understanding this rapidly changing and particularly complicated period of life.

Research in the following areas could contribute to the general knowledge base about developmental immunology and provide some insight about the role of infection in SIDS:

- The biologic and immunologic role of the several types of white blood cells;
- Effects of drugs administered during pregnancy, labor, and delivery, and in early infancy on immune

response mechanisms in the fetus, the neonate, and the young infant;

- Specific immune responses of newborn and weanling mammals, including humans, to pathogenic agents that cause upper respiratory infections, diarrhea, and other common diseases of young infants;

- Longitudinal studies of immune status in infants at high and low risk for SIDS and who have had serious infections such as septicemia and meningitis, to determine whether such experiences with infection impede or promote the development of appropriate immune responses; and

- The impact during pregnancy of such infectious agents as cytomegalovirus and Group B beta-hemolytic streptococcus on immune-response mechanisms of neonates and of infants older than 1 month.

Broadening the base of biological knowledge in the areas of developmental immunity and infection could promote information not only on problems of SIDS but also on problems of pregnancy and infancy with analogous immune-response aberrations.

Metabolic Factors

Within the past decade, there have been significant advances in understanding the metabolism and biochemical properties of biogenic amines in general and their relationship to specific neurologic disease states in particular.[75] One monoamine system, which has been well characterized, consists of an overall sequence in which phenylalanine is converted successively to tyrosine, dopa, dopamine, norepinephrine, and epinephrine, with the latter being converted to metanephrines and vanillylmandelic acid (VMA). In this pathway, dopamine may also be converted to homovanillic acid. Indeed, this is the major metabolite that appears in the urine when L-dopa is administered. Another monoamine system consists of the conversion of tryptophan to serotonin (5-hydroxytryptamine), which is further metabolized by deamination and oxidation to 5-hydroxyindoleacetic acid (5-HIAA).

Although the relationships between these monoamine systems and the control of respiration have not been developed in detail, there are hints from clinical experience that a relationship may exist. Individuals who have episodes of apnea or chronic hypoxemia, for example, may have

known disorders in neurotransmitter metabolism, such as pickwickian syndrome, narcolepsy, or parkinsonism. On the other hand, toxic amounts of L-dopa, when given to some patients with parkinsonism, will produce a definite hyperventilation. One investigator has explored this general relationship in a setting that may be relevant to SIDS by studying the excretion of monoamine metabolites in the urine of 22 low-birthweight infants, 17 of whom had apneic spells. Compared to the nonapneic controls, the apneic group showed a clear diminution ($p=<0.01$) in urinary dopamine, norepinephrine, and epinephrine, but no significant difference in dopa excretion. While urinary excretion of any of these substances is obviously difficult to interpret precisely in relation to the actual events occurring in the brain, these results nonetheless are suggestive of a possible relationship between abnormalities of neurotransmitter metabolism and respiratory control.

Another piece of information possibly relating to SIDS is a study of a "near-miss" SIDS infant 1 week after an acute episode of apnea. The infant came from a family in which there had already been two SIDS victims. Study of a 24-hour urine collection for monoamine metabolites compared to controls showed a tenfold increase in dopa excretion, with a significant diminution in the excretion of dopamine. Although norepinephrine and epinephrine excretions were similar, vanillylmandelic acid excretion in this patient was markedly reduced. Serotonin excretion was also markedly reduced, accompanied by a decrease in its metabolite, 5-HIAA, but a slight increase in its precursor, 5-hydroxytryptophan (5-HTP). A repeat analysis conducted 2 months later was normal.

These findings suggested a deficiency in L-aromatic amino acid decarboxylase. This enzyme is relatively nonspecific in that it is capable of catalyzing the decarboxylation of a number of aromatic amino acids, such as dopa, 5-HTP, or histidine, to produce the corresponding amines, dopamine, serotonin, and histamine, respectively. Since specific decarboxylases for dopa and 5-HTP have not been demonstrated, a deficiency of this nonspecific enzyme would provide a common link between the dopamine and the serotonin systems, and would thus explain the observed results in this "near-miss" patient.

There is no direct evidence of a simple cause-and-effect relationship between a given nutritional deficiency and a short-term eventuation in death. It is, of course, true that specific deficiencies of such nutrients as vitamins or trace minerals may produce death in animals, but there are no known cases where a clear, more or less specific, morphologic lesion is not at least demonstrable. If

nutrition plays a role at all in SIDS, it is far more likely that it is a subtle one in which a given, probably subclinical, deficiency occurs, possibly related to income level.

The provocative observation that the livers of SIDS victims have contained a markedly reduced activity of the enzyme phosphoenolpyruvate carboxykinase (PEPCK) has focused attention on the possibility of a defect in carbohydrate metabolism as an etiologic factor in SIDS. PEPCK is one of four key gluconeogenic enzymes; the other three are pyruvate carboxylase, fructose 1,6-diphosphatase, and glucose 6-phosphatase. The role of PEPCK in SIDS, however, remains unclear.

Upper Airway Factors

The anatomy of the human neonate is strikingly different from that of the older child. In the infant, the relatively large tongue is in apposition to the palate, and the mouth is not yet a chambered structure suited to function as an airway. The panniculus of the cheeks supplements the bony skeleton in providing structural support. The points of apposition between tongue and palate and between the palate and posterior pharyngeal wall, which are critical for proper upper airway functioning, change between term infancy and childhood.

Major changes in anatomy, particularly in spatial relationships, are probably occurring during the period of maximum susceptibility to SIDS. To understand the nature and timing of these changes, normative postmortem material and comparative developmental data from primates are needed for study.

The airway in the pharynx and the upper part of the larynx is maintained by muscular activity. It has been suggested that this mechanism may fail and that the airway may collapse in obstruction. An alternative mechanism, of active laryngeal closure, has also been proposed: this active nonvocal closure, or laryngospasm, is clinically more subtle in infants than in children or adults. Laryngeal, pharyngeal, and nasal sensory cues are important in the regulation of pharyngeal, laryngeal, and thoracic respiratory functions.

The blood and lymphatic vessels of the palate and tongue have been studied by antemortem intravascular injections of dye into dogs and by postmortem injections in human fetuses and adults. They show a general pattern of extremely dense vessels, arranged so that substances absorbed

through the mucosa in one area are rapidly spread in the submucosa over a very large area. In the palate, veins do not parallel the arteries, and venous drainage is posterior and downward to the throat. These relationships must be kept in mind in experiments that attempt a fine localization of the oral pharyngeal receptors that influence respiration when they are stimulated. It is possible, at least theoretically, that stimulants can spread rapidly from the site of initial application to receptors in more distant areas of the upper airway.

Embryologic studies have shown that migrating neural crest cells contribute to the upper airway structure and function in several ways. Besides contributing to the formation of components of the autonomic nervous system, they become sensory receptors in the facial and pharyngeal region. It is possible that abnormalities of these migrating cells will manifest themselves as abnormalities of microstructure, particularly of neural elements, which may be seen at birth but may also be associated with later impairments of function in infant development.[76]

The differentiation of specialized sensory receptors of the upper airway mucosa follows separate schedules. Receptors in the mucosa of the tongue and palate, for example, have a configuration similar to Meissner corpuscles, which seem to develop by interaction between cells already in the area (possibly derived from migrated neural crest cells) and sensory fibers when they reach the area. In the 5- to 6-month-old fetus, differentiation of these receptors is still in its early stages; at the same time, the sensory innervation of the laryngeal aspect of the epiglottic mucosa, which has a different configuration, is quite advanced. The mucosal sensory receptors of the upper airway continue in developmental differentiation during infancy. The schedule of this differentiation varies within the larynx and pharynx. Their differentiation progresses more rapidly in the laryngeal mucosa, probably because this is a critical site of sensory as well as motor performance.

The larynx and possibly other regions of the upper airway contain receptors sensitive to relatively high concentrations of carbon dioxide. The nature of these chemoreceptors is not clear, but their failure to function properly has been implicated as a cause of SIDS. In addition, the human larynx contains a set of glomus bodies that are histologically similar to the carotid body, which might serve a chemoreceptor function.

Full-term infants decrease their breathing movements when they breathe oxygen. The implication is that, when newborn infants breathe air which contains 21 percent oxygen,

chemoreceptors are stimulated. There is a temporary increase in breathing movements when newborn infants breathe less than 21 percent oxygen. As they continue to breathe a hypoxic gas, breathing movements decrease below normal levels. In contrast, adults breathing air containing less than 21 percent oxygen have a sustained increase in breathing movements. So, while the peripheral chemoreceptor reflexes appear to be operating in the newborn infant, they do not appear to be as active as they are in the adult. The variation between individuals, however, is great. At the same gestational and postnatal age, some infants show a prolonged increase in breathing movements when they breathe hypoxic gas mixtures, whereas others have little or no initial increase in ventilation and almost immediately have a profound decrease in ventilation. How these differences relate to susceptibility to SIDS remains unclear.

The mucosa of the epiglottis and vocal folds contain receptors that when stimulated can produce apnea in sheep that sometimes progresses to death. These receptors are sensitive to some fluids, most notably distilled water, but not to others, such as saline. The typical response to stimulation includes apnea, bradycardia, hypertension, and usually swallowing.[77] When it occurs, swallowing appears to act as a protective mechanism by removing the stimulant from the upper airway.

This phenomenon was first noticed in fetal and neonatal lambs. The response is weak in adult sheep but remains dependent on the type of fluid touching the laryngeal side of the epiglottis. Although diminishing with age, the phenomenon, which is more prominent in some strains of sheep than in others, is still quite strong in lambs beyond the newborn period, and it is likely to be lethal to lambs since they tolerate asphyxia less well than do newborn infants. Whether the animal will escape or die cannot be predicted by tests of respiratory responses to hypoxia or hypercarbia. Whether a similar system of receptors with the capability of inducing apnea exists in young infants is not yet known. If it does exist, regurgitation of liquefied foodstuffs might precipitate a SIDS event.

Information from animal and human studies suggests that when the upper airway is subjected to any of several external stimuli, the response includes changes in respiration. The response changes with growth and development, and in early postnatal development in many species, a phase occurs that includes prolonged apnea. The duration of the apnea varies not only with the species and age but also between subjects within a species at a certain age. The response is also affected by sleep state. It is not clear whether those with the most prolonged apnea are abnormal or whether they

represent one extreme of normal variation. In the most extreme episodes, the animal dies unless the centers that control respiration override, or escape, the apneic response to reestablish respiration.

Almost every aspect of upper airway structure or function discussed above changes with development or is suspected of doing so. To date, fundamental studies of the developmental processes involved have not focused on the period of development where the highest incidence of SIDS has been reported.

Behavioral Factors

Behavioral components of SIDS have received little attention. Most interest has been focused on grief of parents, siblings, and other relatives, with emphasis on coping behaviors in adjusting to the loss. Anecdotal reports indicate that many parents and older siblings react to the loss of the SIDS infant with prolonged grief and guilt. No systematic studies have yet been undertaken concerning the impact of social, cultural, and sexual factors on the grieving process or on coping with the loss of a family member who dies suddenly and unexpectedly from no apparent cause.

Families, neighbors, representatives of the institutions of society, and the community at large show a strong tendency to assign blame for a SIDS event. In some cases it is directed toward a physician who had recently examined the child and found nothing wrong. More often, it is directed toward the parents or a babysitter. At the least, they suffer from "spoiled identities," and at the worst, they are directly accused of child abuse or neglect. Cross-cultural studies might suggest ways of making SIDS a less lonely and traumatic experience through more supportive community attitudes and interventions.

There are other questions of a behavioral nature that need to be addressed beyond those related to grief and to coping with family loss. Infants at highest risk of SIDS are those born weighing less than 5-1/2 pounds to young mothers who smoke. This epidemiologic observation raises a number of questions. Smoking has been associated with poor pregnancy outcome in a number of studies, and so has young maternal age. Smoking and young maternal age may have behavioral links in terms of life style that have not yet been fully explored.

III. Recommended Research

Epidemiology

Identification of risk factors from previous epidemiologic studies and especially from the NICHD Cooperative Epidemiologic Study of SIDS risk factors is an important element in defining the directions of future research. Although associations observed in retrospective epidemiologic surveys do not provide direct evidence of mechanisms involved in causing an effect, the surveys may help identify new possibilities or indicate the degree of likelihood that certain associations may be involved and therefore should be investigated.

Infection and Immunology

The roles of altered development of the immune response and of infection as a major factor in some cases of SIDS and as a contributing factor in others remain undefined, and further research to formulate testable hypotheses deserves support.

The relationship of silent infections during pregnancy to SIDS in affected infants remains unclear. Research on the impact of cytomegalovirus and adenovirus infection during pregnancy on neonatal and infant health may provide clues to the trigger effect of such infections in SIDS.

Further studies are needed in order to better understand the influence on allergic response of the autonomic nervous system and of the endocrine system, acting singly or together.

Metabolic Factors

Increasing evidence suggests that metabolic defects, especially in the relationship of monoamine systems to the control of respiration, may be involved in some cases of SIDS. It will require further study to develop appropriate controls. Administrative arrangements that would reduce distortions from postmortem changes are also needed.

Upper and Lower Airway

Detailed study of the anatomy and physiology of the upper and laryngotracheal airway in human neonates and in

experimental animals, especially fetal and neonatal lambs, reveals developmental changes that could be involved in some cases of SIDS. Empirical studies of human infants involve the application of findings in experimental animal models.

Behavioral Considerations

Until knowledge of pathogenesis and etiology makes its prevention possible, almost all of the behavioral considerations of SIDS concern the family and the community where it occurs. A better understanding of the theoretical and practical aspects of these behavioral factors must continue to be a focus for research. Specific questions and scientific methods for seeking answers should replace anecdotal information. Although altered behavior in SIDS infants (passivity) has been observed, the possibility that behavioral aberrations in young infants might play an etiologic role in SIDS has not been suggested. The role of lifestyle in affecting pregnancy outcome and fetal and infant health is an area that also needs to be studied.

Sleep

A promising area of SIDS research includes a more fundamental understanding of sleep, particularly the effect of sleep and sleep states on ventilation, blood gases, heart rate, cardiac output regulation, threshold for arrhythmias, blood pressure regulation, and metabolic activity. More information is needed on the role of sleep on gastroesophageal motility, regurgitation, and aspiration; on the modulation of upper airway receptors activity; and on chemical control of breathing. More data are needed on developmental factors that influence arousal or the waking response.

Biochemical Factors

Research is needed on the biochemical basis for apnea, hypoventilation, hyperventilation, and periodic breathing, on the role of potential chemical mediators (catecholamines, substance P, angiotensin, bradykinin, endorphins, amino acids, acetylcholine, serotonin, gamma-aminobutyric acid) in the response to hypoxia and hypercapnia, and on the biochemical basis for changes in cardiac output, heart rate, blood

pressure, and arrhythmia formation during hypoxia and hypercapnia. More information is also needed on the biochemical basis for induction and maintenance of sleep and sleep states, including developmental aspects.

Central Nervous System

Investigations are needed on specific injury patterns in the brainstem and possibly higher CNS centers in SIDS victims.

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